Remarks

I. Status of the Claims

Upon entry of the foregoing amendment, claims 109-110, 112-115, 118-121, 125-128, 132-142 are pending in the application, with claims 109, 110, and 118 being the independent claims. Claims 109, 110, 118, 133, 134, and 138 are amended. Claims 111, 116-117, 122-124, and 129-131 are canceled. Claims 1-108 were canceled previously. These changes are believed to introduce no new matter, and their entry is respectfully requested.

II. The Amendments

As amended, the pending claims are directed to a glycoengineered, recombinant antibody comprising an IgG Fc region containing N-linked oligosaccharides, wherein the antibody is isolated from a *Chinese hamster ovary cell* and has been engineered to have *a majority of said N-linked oligosaccharides that are nonfucosylated*, and wherein said antibody has increased Fc mediated cellular cytotoxicity (claim 109) or, alternatively, increased Fc receptor binding affinity (claim 110) as a result of said engineering. Claim 118 has been amended to recite that the antibody is isolated from a *Chinese hamster ovary cell* and *has been engineered to have an increased proportion of GlcNAc residues to fucose residues in the Fc region.*

Support for these amendments can be found *inter alia* in previous claims 123 and 131, and in the specification as filed at page 22, line 33, through page 23, line 26, and page 37, line 22, through page 38, line 14, and in FIG. 9. Accordingly, no new matter is believed to have been added by the amendments, and their entry is respectfully requested.

III. Brief Description of the Invention

In the broadest embodiments presently claimed, the invention is directed to a glycoengineered, recombinant antibody comprising an IgG Fc region containing N-linked oligosaccharides, wherein the antibody is isolated from a *Chinese hamster ovary cell* and has been engineered to have *a majority of said N-linked oligosaccharides that are nonfucosylated*, and wherein said antibody has increased Fc mediated cellular cytotoxicity (claim 109) or, alternatively, increased Fc receptor binding affinity (claim 110) as a result of said increased proportion of nonfucosylated oligosaccharides. This invention is the result of Applicants' discovery that the oligosaccharides that occur in the Fc region of antibodies, such as IgG, can be engineered, by a variety of methods, to produce non-naturally occurring *variant* oligosaccharide conformations that have been found to dramatically increase the antibody effector function, such as antibody-dependent cellular cytotoxicity (ADCC), as well as the antibody's affinity for Fc receptors.

Typically, there is heterogeneous processing of the core oligosaccharide structures attached at a particular glycosylation site, so that even monoclonal antibodies exist as multiple glycoforms. By engineering the host cells that produce the antibodies to favor production of an antibody having a variant oligosaccharide conformation in the Fc region, *i.e.*, having a significant increase in the proportion of nonfucosylated oligosaccharide structures, Applicants are able to generate variant glycoforms of the antibody having oligosaccharide conformations that are *not otherwise capable of being produced by the host cell* and which exhibit dramatically increased ADCC and Fc receptor binding compared to the corresponding nonglycoengineered antibody.

IV. The Rejections

A. The Rejections Under 35 U.S.C. § 112, Second Paragraph

At page 2 of the Office Action, the Office has rejected claims 109-142 as being indefinite for failing to particularly point out and distinctly claim the invention. In particular, the Office asserts that claims 109, 110, and 118, and the claims dependent thereon, are indefinite in the recitation "the corresponding antibody produced by the same host cell that has not been glycoengineered" because there is no antecedent basis for "the same host cell" and the basis for comparison is not clear. Applicants respectfully traverse the rejection.

As mentioned above, the essence of Applicants' invention was the discovery that host cells could be engineered to produce glycoengineered antibodies which bear completely novel oligosaccharide structures not previously obtainable from said cells absent the glycoengineering and which have substantially increased effector function (e.g., ADCC) and Fc receptor binding. Applicants submit that one of skill in the art would understand the claim language in question to be referring to the comparison between the oligosaccharides structures of the glycoengineered antibodies produced by the engineered host cells compared to the antibodies produced by the nonengineered host cells.

Nevertheless, without acquiescing in the propriety of the rejection, and solely in the interests of advancing prosecution, Applicants have amended the claims to eliminate the language questioned by the Office. Accordingly, the ground for rejection is moot and the rejection may be withdrawn.

The Office has also rejected claims 111, 116 on the ground that there is insufficient antecedent basis for the phrase "the predominant N-linked oligosaccharide."

As claims 111 and 116 have been canceled, the rejection is now moot. Also, the rejection of claim 117 on the ground of lack of antecedent basis for the phrase "the corresponding antibody" has been rendered moot by the amendment to the claims.

The Office asserts that claim 118 is unclear in the recitation in that "[t]he claim recites two different proportions and only one basis for comparison." Applicants point out that claim 118 as amended now recites "an increased proportion of GlcNAc residues to fucose residues in the Fc region." One of skill in the art would readily understand that this refers to an increase in the number of GlcNAc residues relative to the number of fucose residues in the Fc region. Accordingly, the claim is sufficiently clear and precise that the rejection may be withdrawn.

Finally, the Office has rejected claims 130-132 on the ground that there is insufficient antecedent basis for the phrase "the majority of N-linked oligosaccharides." Applicants have canceled claims 130-132, and the relevant remaining claims now recite "a majority . . ." Thus, the rejection is moot and should be withdrawn.

B. The Rejection Under 35 U.S.C. § 112, First Paragraph

At page 4, the Office has rejected claims 109-142 as failing to comply with the written description requirement on the ground that the claims contain new matter. Specifically, the Office identifies several limitations in the pending claims and asserts: "No such limitations are found in the claims as originally filed in this application . . . . There is no support for such broad limitations, or evidence that applicants considered such limitations as part of their invention, in the parent application, . . . thus the instant claims comprise New Matter." (Office Action at pages 4-5.) Applicants traverse the rejection.

First, Applicants point out that whether the limitations at issue were present in the *claims* as originally filed is not the proper inquiry. Rather, all that is required is that the currently pending claims are adequately supported by the *disclosure* as filed. Second, Applicants have previously identified specific support in the application for each of the claim limitations that the Office questions. (*See* Amendment and Reply filed July 18, 2005, at page 14, and Amendment and Reply filed July 24, 2006, at pages 9-10.) The Office has made no attempt address the sufficiency of the specific support for these claim limitations cited by the Applicants.

The Office's rationale underlying the new matter rejection appears to be that "[n]on-fucosylated oligosaccharides are only mentioned in reference to a single example of specific antibody produced in modified CHO cells . . . and are not disclosed as correlated with an increase in ADCC for this antibody, or for antibodies in general." (Office Action at page 5.) The Office, however, has misinterpreted the teachings of the application. Specifically, decreased fucosylation is a necessary characteristic of the claimed glycoengineered antibodies, because oligosaccharides which are first modified by GnT III can no longer serve as biosynthetic substrates for the core α-1,6-fucosyltransferase responsible for transferring the fucose residue to the N-linked oligosaccharide of the antibody. This is specifically mentioned in the original application as filed (*see* page 38, lines 4-5). Moreover, this fact was well-known to those skilled in the art at the time the original application was filed. *See* Schachter *et al.*, *Biochem. Cell Biol. 64:163-181 (1986).* Thus, the application explicitly disclosed this aspect of the claimed antibodies.

Even if the application had lacked this explicit teaching, the application would nevertheless necessarily have disclosed the claimed antibodies with increased non-

fucosylated oligosaccharides because this is an *inherent characteristic* of the antibodies of the invention. Specifically, because the presence of the bisecting GlcNAc residue introduced by GnT III blocks attachment of the fucose residue by the core α-1,6-fucosyltransferase, the claimed antibodies with increased ADCC necessarily have reduced fucosylation. "From the standpoint of patent law, *a compound and all of its properties are inseparable*; they are one and the same thing." *In re Papesch*, 137 USPQ 43, 51 (CCPA 1963) (emphasis added). Thus, "[t]he disclosure in a subsequent patent application of an inherent property of a product does not deprive that product of the earlier filing date. *Nor does the inclusion of a description of that property in later-filed claims change this reasonable result.*" *Kennecott Corp. v. Kyocera International, Inc.*, 5 USPQ2d 1194 (Fed. Cir. 1987), *cert. denied*, 486 U.S. 1008 (1988) (finding claims of CIP entitled to benefit of priority application even though limitation was not explicitly found in earlier application where limitation was found to be inherent characteristic of composition disclosed in earlier application.) Accordingly, increased nonfucosylation was both an inherent feature of the glycoengineered antibodies as well as explicitly disclosed in the priority application.

The other limitations that the Office contends are new matter are likewise fully disclosed by the application. Because GnT III attaches a bisecting GlcNAc to the N-linked oligosaccharide structure, the claimed antibodies necessarily have increased GlcNAc residues relative to fucose residues. Moreover, the glycoengineered antibodies do not contain a significant amount of high mannose structures.

In view of the above, Applicants respectfully submit that all of the claims are sufficiently supported by the application, and the rejection must be withdrawn.

C. The Rejections Under 35 U.S.C. § 102

1. Kilmartin et al.

At page 6 of the Office Action, the Office has rejected claims 109, 110, 114, 117, 122-124, 131, 133, 135, 136, and 140-142 under 35 U.S.C. § 102(b) as anticipated by Kilmartin *et al.*, *J. Cell Biol.*, 1982, as evidenced by Shinkawa *et al.* (*J. Biol. Chem.* 2003). The Office relies on Kilmartin *et al.* as teaching a rat antitubulin monoclonal antibody produced in YB2/0 cells. The Office relies on Shinkawa *et al.* as teaching that because YB2/0 cells express low levels of fucosyltransferase, the antibodies of Kilmartin *et al.* must necessarily have greater nonfucosylated residues. According to the Office, the functional limitations of the claimed antibodies and the glycan structure were inherent properties of the Kilmartin antibody. Applicants respectfully traverse the rejection.

No mention is made in Kilmartin *et al.* as to glycoengineering of antibodies. Moreover, no mention is made of the ADCC of the antibody at all. Nevertheless, without acquiescing in the rejection, and solely to advance prosecution, Applicants have amended the claims to now recite glycoengineered antibodies isolated from engineered *CHO cells*. Because Kilmartin *et al.* discuss the production of an antibody in YB2/0 cells, and not CHO cells, the present claims are not anticipated by Kilmartin *et al.* Thus, the rejection should be withdrawn.

2. Rothman et al.

The Office has also rejected claims 109-111, 114, 122-128, 131, 133, 135-136, 138, and 140-142 as anticipated by Rothman *et al. Mol. Immunol. 1989* as evidenced by Shields *et al.* and Wright *et al.* Applicants traverse the rejection.

As noted above, the claims as amended now recite glycoengineered antibodies produced by CHO cells. Rothman *et al.* fail to teach a glycoengineered antibody with increased ADCC produced by a *CHO* cell. Thus, the claim rejection has been obviated, and should be withdrawn.

C. The Double-Patenting Rejection

The Office has issued several *provisional* double patenting rejections. As these rejections are only provisional, Applicants again request that they be held in abeyance until allowable subject matter is identified.

Conclusion

Prompt and favorable consideration of this Reply is respectfully requested. Applicants believe the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Respectfully submitted,

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